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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

WARNING LETTER

Federal Express

Charles O. Dotson, Ph.D.
Department of Kinesiology
College of Health and Human
Performance
University of Maryland
2142 HLHP, Building 255
College Park, Maryland 20742

Re: [REDACTED]
Investigational Studies
[REDACTED]

Dear Dr. Dotson:

During the period of August 26 through October 20, 1997, you were visited by Ms. Nancy L. Rose, and Mr. Patrick V. McCarthy, investigators from the Baltimore District Office of the Food and Drug Administration (FDA). The purpose of FDA's inspectional visit was to determine whether your activities as an investigator for [REDACTED] investigational device, [REDACTED] complied with applicable regulations. This product is a device as that term is defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

This inspection was conducted under a program designed to ensure that data and information contained in applications for Investigational Device Exemptions (IDE), Premarket Approvals (PMA), and Premarket Notification [510(k)] submissions are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of the scientific investigation.

The requirements for investigational device studies, Title 21, Code of Federal Regulations (21 CFR) Part 812-Investigational Device Exemptions, Subpart E-Responsibilities of Investigators and Subpart G-Records and Reports, and Section 520(g) of the Act, were used as guidance to audit your studies. The deviations that were noted during the inspection were listed on Form FDA-483, "Inspectional Observations," which was presented to and discussed with you at the conclusion of the inspection.

We acknowledge receipt of a copy of your December 15, 1997, written response sent to the Compliance Director, Baltimore District Office, which addressed each of the inspectional observations (FDA-483). Based on our review of the inspectional report, we identified the following deviations listed below. In addition, our review of your written response has revealed inconsistencies and/or the need for your further clarifying matters associated with these deficiencies:

1. **General Responsibilities of Investigators [812.100]:** An investigator is responsible for ensuring an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations; for protecting the rights, safety and welfare of subjects; and for control of devices under investigation.

The inspection revealed deficiencies relating to each of the general responsibilities of investigators; however, during the inspection and in your written response you indicate that you did not know that your data were to be submitted to FDA until after the study was completed and that you do not consider yourself a clinical investigator.

Please be aware that your participation as an investigator defined in 21 CFR 812.3(i), for the conduct of an investigation, is established. You conducted an investigation involving one or more human subjects using [REDACTED] devices to determine their effectiveness, and you are therefore an investigator who is required by Federal Law to ensure adherence to the requirements of the Act and applicable regulations.

2. **Investigator Records [812.140(a)]:** A participating investigator shall maintain accurate, complete, and current records relating to the investigator's participation in an investigation. The following records were not available for inspection:

- a) **Correspondence demonstrating that protocols and informed consent documents for the reported studies were reviewed and approved prospectively by an IRB [21 CFR 812.140(a)(1)].**

The FDA investigators requested documentation showing that an IRB had prospectively approved protocols and consent forms for two reported studies, [REDACTED] and [REDACTED]. You stated that you revised the protocols for these two studies and that a revised protocol was approved. However, during the inspection you did not provide these revised protocols or consents. Instead, you provided the FDA investigators records for a study proposal and consent forms for

an investigation entitled, "[REDACTED]", that was prospectively approved by your departmental review committee. That study differed from your reported studies in that it involved tests measuring the subject's residual volume, hydrodensitometry, total body water involving consumption of deuterium oxide and two blood tests, skinfold measurements, and testing as related to [REDACTED].

Your subsequent written response to FDA-483 Items 5a and b provides clarification that the investigation involved the use of the [REDACTED] devices, and that only portions of the data from [REDACTED] devices were reported to FDA. Your response appears to explain why the protocol and consent documentation that were provided during the inspection were not consistent with the reported studies.

In your written response to FDA-483 Item 2, you state that a revised protocol was submitted to [REDACTED], however, you did not provide any supporting documentation of the revised protocol and correspondence with your sponsor.

Please provide copies of the revised protocols for the two reported studies and supporting documentation demonstrating that these two revised protocols had been prospectively approved by your sponsor and an IRB in compliance with 21 CFR Part 56-Institutional Review Boards.

Further, you state in your written response to FDA-483 Item 2 that you consulted with the Department of Kinesiology representative to the IRB, [REDACTED], who advised you that changes or revisions of the protocol did not require a second IRB approval. The documentation that you provided during the inspection, a "Human Subjects Proposal Sheet," dated February 4, 1996, indicates that your [REDACTED] device investigation was not submitted to the campus-wide Institutional Review Board (IRB) for an initial approval, but that it was approved by the Department of Kinesiology Committee for Research on Human Subjects.

Please provide a copy of a written charter and operation procedure, or other documentation which shows that your institution, The University of Maryland, has recognized the Department of

Kinesiology Committee for Research on Human Subjects as an IRB duly constituted in compliance with FDA regulations 21 CFR Part 56 to approve human studies involving FDA regulated investigational articles, such as devices and drugs.

- b) Correspondence or other written documentation with your sponsor to show your commitment to conduct the investigation in accordance with an approved investigational plan, study protocols, and compliance with applicable FDA requirements [21 CFR 812.100 and 812.140(a)(1)].**

During the inspection, and in your December 15 letter, you state that you were unaware that the results of these experiments were for submission to FDA until after the study was completed, which is consistent with the inspectional observation that a written investigator agreement was not maintained as part of your study records.

However, your letter also indicates that you included only [REDACTED] in the reports submitted to FDA, and that information for the [REDACTED] was transposed to separate data sheets for submission to FDA, because the [REDACTED] data were "irrelevant" to the [REDACTED]. These statements appear to indicate that you may have selectively prepared the data and reports with a specific FDA submission in mind.

Please describe when and how you first learned that your study was for FDA submission, and any instructions you may have received concerning data which needed to be reported to FDA—or be excluded from the report—and the reasons why. Include a description of your understanding of how the study results would be used [REDACTED] if not for submission to FDA.

- c) Records documenting the receipt, use, or disposition of the investigational device or devices, which relate to: the type and quantity of the device, the dates of its receipt, and the batch number or code mark; the names of all persons who received, used, or disposed of each device; and, why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed [21 CFR 812.140(a)(2)].**

During the inspection you stated that you could identify the [REDACTED] device used in the submitted studies; however, records necessary for determining the serial number of the device used were not observed in the records you provided for inspection.

In your written response to FDA-483 Item 1a, you state that for all measurements the serial number of the specific device used was recorded on each data sheet. The data sheets that were inspected do not contain the serial numbers of the devices used; therefore, we must conclude that the records described in your response letter may not have been provided for inspection.

Please provide copies of all data sheets showing serial numbers of devices used for each subject's measurements, with an explanation to indicate why the raw data sheets provided for inspection lacked device serial numbers.

- d) Records demonstrating that signatures appearing on informed consent documents were obtained prior to participation in the study, for subjects who are identified solely by numbers in the study records [21 CFR 812.140(a)(3)(i)].**

During the inspection you stated that you could verify that each subject signed an informed consent form; however, records that are necessary to conduct such verification were not among records you provided for inspection.

In your written response to FDA-483 Item 6, you state that you can verify every informed consent by name and subject ID, by referring to data sheets for the [REDACTED]. The data sheets described in this response for verification of consents were not previously provided during the inspection.

Please provide copies of all records relating to the investigation described in your written response, including the records showing consent verification.

- e) Records documenting that pre-study health histories required for study entry or exclusion were obtained from each subject [21 CFR 812.140(a)(3)(ii)].**

During the inspection you denied that the health histories were documented; however, in your written response to FDA-483 Item 5a, you

state that the screening health history questionnaires were completed by each subject and that these data collection forms were retained for the [REDACTED]. These forms were requested several times during the inspection; however, they were not provided to the FDA investigator.

Please provide copies of the records and data collection forms for all subjects described in your response letter, including copies of the pre-study health history screening questionnaires and data collection forms for each of the subjects.

- f) Records documenting exposure to the investigational device, including the date and time of each subject's exposure to the device [21 CFR 812.140(a)(3)(iii)].**

During the inspection you indicated that these records were not maintained; however, in your written response to FDA-483 Item 5b you state that you maintained records showing the dates of the subjects' exposure to the devices. Also, in response to FDA-483 Item 1a you state you maintained records documenting the serial number of the device used for each measurement recorded on each subject's data sheet. These records which are described in your responses appear to be study records relating to your investigation that may have not been provided for inspection.

Please provide copies of all records for each subject, including exposure to all devices that were used during the investigation.

- g) The protocol, with documents showing the dates of and reasons for each deviation from the protocol [21 CFR 812.140(a)(4)].**

See discussion above under 2(a). You did not provide copies of the prospective protocols for the two submitted studies during the inspection.

Please provide copies of prospective (approved/ revised) protocols referenced in your response, and documentation of deviations from the approved protocols.

- 3. Investigator reports [812.150(a)]. An investigator is required to prepare and submit a complete, accurate, and timely final report to the sponsor of the study [812.150(a)(6)].**

The final study reports that were submitted are entitled, "[REDACTED]"

and "[REDACTED]"

In your written response, you state that your study was entitled, "[REDACTED]"

"Your letter indicates that the study was planned and conducted "... with the view to insuring a high degree of both internal and external validity." In responding to FDA-483 Item 1a, you explain, "... our experiments included two devices, the [REDACTED]" and "We tested all subjects with both devices, although only data from the [REDACTED] were submitted to FDA."

These submitted reports are incomplete, because they do not state that your study actually involved gathering data from the same subjects using [REDACTED] device as a planned part of the study. Further, the reports do not reflect that the [REDACTED] data are excluded.

We note that your institution's authorization of a human study proposal specifically identifies that both [REDACTED] devices are used for the research. We therefore would expect a final study report showing the results obtained from each test performed on each human subject and including all devices used.

In your response to FDA-483 Item 5b, you state that "Because data from the [REDACTED] are irrelevant to the [REDACTED], only data from the [REDACTED] were submitted to the agency." A report of the complete study described in your written response was not submitted to the agency for evaluation; and a complete set of the original study records were not supplied for FDA inspection. Without access to a complete study report and access for inspection and verification of all data and records relating to this study, we cannot verify the validity of your assertion that the [REDACTED] data are "irrelevant."

4. In the absence of adequate and complete study records and reports (as indicated above) your study staff described to FDA investigators experimental procedures and records that were maintained during the study, which did not coincide with records and reports that were provided for inspection, as follows:

- a) Your study staff stated that several [REDACTED] devices were used during the studies. Two of your staff indicated that they had used [REDACTED] and

[REDACTED] devices on each subject. The staff described distinguishing physical characteristics of devices used, which they termed as "older" and "newer" models. The features they described involve different wand configurations (housings of the UV emitters and receptors), keyboard operation, and computer hook-up capability. In contrast with the statements made to FDA by your staff, your statements during the inspection and the study records provided for inspection showed only that a [REDACTED] was studied.

We have noted that in your response letter you revealed that the study involved more than one device, and your response is consistent with the statements made by your staff.

Your written response also states, "Appropriate information for the [REDACTED] [REDACTED] was transposed to a separate data sheet that was submitted to FDA along with the other relevant data for the [REDACTED] [REDACTED]." Please provide a description for further clarification of the procedures that were followed for data handling for the [REDACTED] as opposed to the [REDACTED] during the study; and describe how, and by whom, the decision was made to transpose the [REDACTED] data to separate "raw data" sheets that were submitted to FDA. Who did the transposition of the data? Please provide a description and copies of any notes or written instructions that were received or given concerning this activity.

The FDA investigators requested that you provide all records relating to your investigation for comparison with the submitted reports to assess their accuracy and reliability. The data sheets that you provided during the inspection appear to contain the same information as the data sheets supplied to FDA in a December 31, 1996, submission to the Center's Office of Device Evaluation. However, your written response to FDA-483 Items 1a, 2, 4, 5, and 6, describes additional source records relating to your investigation which you apparently did not supply for inspection. Please note that 21 CFR 812.145(b) requires an investigator to permit authorized FDA employees to inspect and copy all records relating to an investigation.

- b) Your study staff stated that subjects completed written health history questionnaires which were given to you for review and retention. Your report indicates that the pre-study health histories were obtained; however, you stated during the inspection that health histories were taken verbally by your staff without written documentation. We have noted

that in your response to the FDA-483 you indicate that written health questionnaires were obtained. Please explain why you said, during the inspection, that you did not obtain these records. As indicated earlier in this letter, please provide copies of each of the subject's history records.

- c) Your study staff described procedures for using one type of [REDACTED] device and explained that they recorded the subjects' test results in handwriting. However, there were no handwritten test results for subjects' observed in the study records that you supplied for inspection. Please provide your explanation concerning this inconsistency and copies of the records of those test results.**
- d) Your study staff described instances in which the residual volume tests were repeated for some subjects, and that there was a mechanical failure of the testing apparatus. Repeat tests and apparatus failures are not represented in your final reports. Records of repeat tests and apparatus failures were not found with your study records that were inspected. We have noted that your written response includes an explanation concerning this inconsistency and we request that you provide us copies of records of the events described.**

Further, we received a report from the Baltimore District Office that, on January 23, 26, 27, and 29, 1998, Ms. Nancy L. Rose contacted your office to schedule a second inspection. The purpose of the second inspection was to follow up on your December 15, 1997, letter which referenced some of your study records that apparently were not revealed to FDA during the initial inspection. On January 30, 1998, you telephoned Ms. Rose, who informed you of the purpose of the second inspection. However, you refused to agree to an inspection date and requested that she provide a written list of queries to you prior to scheduling a meeting. **This letter is not a list offered in response to your request for one.**

The regulation, 21 CFR 812.145(b), establishes that an investigator shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation. Ms. Rose, in her official capacity, contacted you to arrange a suitable time and place to inspect all records related to your [REDACTED] device investigation. You should be aware that any failure to provide all records related to the investigation for inspection significantly interferes with, and causes delays in, the completion of FDA's inspection and data audits to assess the accuracy and reliability of the submitted study reports.

Please respond to this office in writing, within fifteen (15) working days of receipt of this letter, to advise us of the specific steps you have taken to address these violations and to prevent similar violations from occurring in current or future studies. Your submission of copies of study records as supporting documentation for your response to this letter does not preclude any inspectional follow-up on all records and reports related to any investigations involving regulated products.

Your failure to respond may result in further regulatory action without notice: FDA regulation, 21 CFR 812.119, describes an administrative procedure for disqualifying a clinical investigator when the agency has information indicating that an investigator has repeatedly or deliberately failed to comply with applicable requirements, or has repeatedly or deliberately submitted false information either to the sponsor of an investigation or in any required report.

Please direct your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2094 Gaither Road, Rockville, Maryland, 20850, ATTN: Mr. Rodney T. Allnutt, Consumer Safety Officer.

A copy of this letter has been sent to the Food and Drug Administration, Baltimore District Office, 900 Madison Avenue, Baltimore, Maryland, 21201. **We request that a copy of your response be sent to that office.**

Please direct all questions concerning this matter to Mr. Rodney T. Allnutt at 310-594-4723, ext. 140.

Sincerely yours,

Michael E. Marcarelli

Lillian J. Gill
Director
Office of Compliance
Center for Devices and
Radiological Health